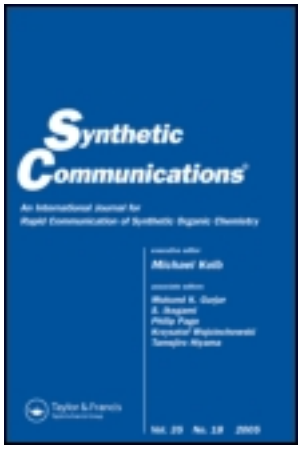

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Tartaric Acid-Catalyzed Synthesis of α-Aminophosphonates Under Solvent-Free Conditions

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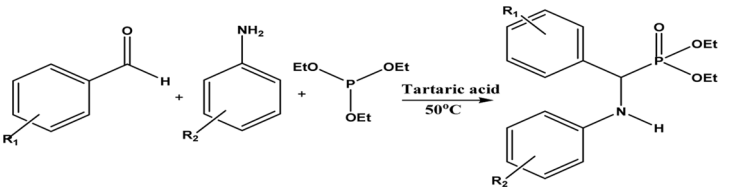
GRAPHICAL ABSTRACT



Abstract *A facile procedure is developed for the synthesis of α-aminophosphonates, using tartaric acid as a stable, environmentally benign, low cost, and easily available organocatalyst. In the presence of tartaric acid (10 mol%), triethyl phosphite reacts with imines (generated in situ from an aldehyde and an amine) to yield the corresponding α-aminophosphonates. The organocatalyst tartaric acid is more stable during reaction. The catalyst provides easier workup, affords better yields, and takes less reaction time in comparison to generally used Lewis acid catalysts.*

Keywords α-Aminophosphonates; organocatalyst; tartaric acid; triethyl phosphite

INTRODUCTION

Because of their structural analogy to α-amino acids, α-aminophosphonates have been the subject of considerable interest. They function as inhibitors of enzymes involved in the metabolism of proteins and amino acids. These compounds have already been found to act as antibacterial agents, neuroactive compounds, anticancer drugs, and pesticides, with some of them being commercialized. The altered activity of such enzymes has been associated with HIV infections and several pathological disorders, including cancer and cataracts.[1]

Organophosphorous compounds have been known for more than 50 years.[2] Many of them exhibit biological activity and are widely used as potent herbicides.

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Perhaps the best known are glyphosate,[3] trakephon,[4] and amino phosphonic acid derivatives of fluorine.[5] It was suggested that the biological activity of these are correlated to their lipophilicity.[6]

Nucleophilic addition of phosphate onto imines, catalyzed by a base or an acid, has emerged as an important alternative for the synthesis of α-aminophosphonates derivatives. Generally, Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3 \cdot OEt_2$, $ZnCl_2$, $MgBr_2$, and $InCl_3$ have been used as catalysts.[7]

However, these reactions could not be carried out efficiently in a single-step operation with the carbonyl, amine, and phosphite functionalities because water formed during imine formation can decompose or deactivate these Lewis acids. There is a need to develop a one-pot synthesis of α-aminophosphonates catalyzed by a water-tolerant Lewis acid.[8]

Organocatalysis has emerged as an important area of research over recent decades.[9] It is well known that organocatalyst tartaric acid is a relatively stable, easy-to-handle solid that is insensitive to small amounts of air and moisture. Herein, a mild and efficient protocol for the synthesis of α-aminophosphonates was undertaken using a catalytic amount of organocatalyst tartaric acid under solvent-free conditions.

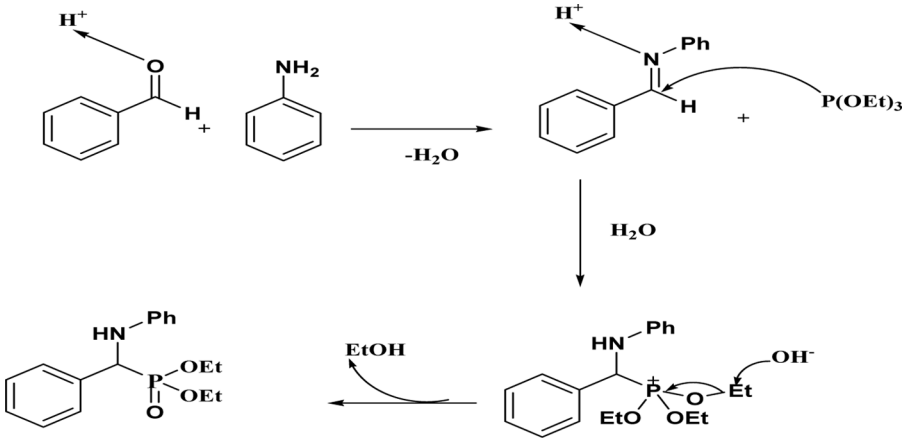
RESULTS AND DISCUSSION

We explored the effectiveness and compativility of tartaric acid as a catalyst for the generation of α-aminophosphonates. Thus, the reaction of triethyl phosphite with imines generated *in-situ* from substituted benzaldehyde and aniline or *p*-anisidine at 50 °C in the presence of 10 mol% of tartaric acid without using any solvent afforded the corresponding α-aminophosphonate in good yield (Table 1). The reaction was completed in 2 h, and the product was isolated by extraction with water and dichloromethane in high purity. To the best of our knowledge, this is the first demonstration of tartaric acid–catalyzed synthesis of α-aminophosphonates.

Several aromatic aldehydes were examined using different amounts of tartaric acid. Finally, it was found that 10 mol% of tartaric acid was optimum to catalyze the

Table 1. Synthesis of α-aminophosphonate derivatives

Compound	R^1	R^2	Yield (%)
A	H	H	83
B	4-OCH_3	H	89
C	2-Cl	H	77
D	4-OH	H	62
E	4-CH_3	H	78
F	4-F	H	71
G	2-OCH_3	H	81
H	3-OCH_3	H	71
I	4-Cl	H	78
J	H	4-OCH_3	65
K	4-OCH_3	4-OCH_3	74
L	2-Cl	4-OCH_3	78



Scheme 1. Mechanism of synthesis of α-aminophosphonate.

reaction efficiently. The results are shown in Table 1. In all cases, the reaction proceeded smoothly to give the corresponding α-amino phosphonates in good yields. Most important, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents including hydroxy groups reacted efficiently, giving excellent, yields. The mechanism of this reaction is believed to involve, at first, the formation of the activated imine so that addition of phosphite is facilitated to afford phosphonium intermediate, which then undergoes reaction with water generated during formation of imine to give α-amino phosphonates and ethanol as shown in Scheme 1.[10]

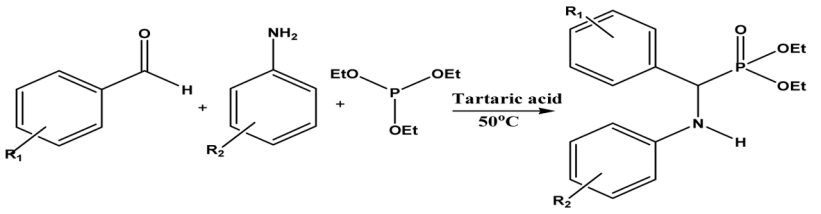
CONCLUSIONS

We have successfully demonstrated the use of tartaric acid as a catalyst, for the first time, to the three-component, high-yielding synthesis of α-aminophosphonates. The tartaric acid is stable and does not show any decrease in its catalytic activity due to *in-situ* generated water during the course of the reaction.

EXPERIMENTAL

A mixture of benzaldehyde (10 mmol), tartaric acid (10 mol%), aniline (10 mm), and triethyl phosphite (11 mm) was stirred vigorously on a magnetic stirrer at 50 °C for approximately 2 h (Scheme 2).

The reaction was monitored from time to time by running reaction mixtures on silica-gel thin-layer chromatography (TLC) plates using a hexane and ethyl acetate (80:20) solvent system. After completion of the reaction, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ and then extracted with dichloro-methane. The organic layer was washed with water and brine. The organic extracts were combined, dried over sodium sulfate or magnesium sulfate, and concentrated under reduced pressure to give the crude products. The residue was purified by recrystallization with chloroform.



R_1= H, 4-Cl, 3-Cl, 4-F, 2-OMe, 3-OMe, 4-OMe, 4-OH, 4-CH_3

R_2 = H, 4-OMe

Scheme 2. Synthesis of α-aminophosphonate derivatives using tartaric acid.

Diethyl(phenylamino)(phenyl)methylphosphonate (A)

IR (KBr), 3392, 1235, 1018, 759 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 1.138 (t, 3H, $J = 7$ Hz, OCH_2CH_3), 1.310 (t, 3H, $J = 7$ Hz, OCH_2CH_3), 3.962 (q, 2H, $J = 7$ Hz, OCH_2CH_3), 4.139 (q, 2H, $J = 7$ Hz, OCH_2CH_3), 4.186 (bs, 1H, NH), 4.793 (d, 1H, CH), 6.610–7.304 (m, 10H, C_6H_5); ^{13}C NMR ($CDCl_3$, TMS): δ 56.67, 63.28, 76.81, 77.06, 77.32, 113.87, 118.41, 127.89, 128.60, 129.18.

Diethyl(phenylamino)(4-ethoxyphenyl)methylphosphonate (B)

IR (KBr), 3373, 1234, 1022, 757 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 1.152 (t, 3H, $J = 7$ Hz, OCH_2CH_3), 1.343 (t, 3H, $J = 7$ Hz, OCH_2CH_3), 3.739 (q, 2H, $J = 7$ Hz, OCH_2CH_3), 3.829 (s, 3H, OCH_3), 4.135 (q, 2H, $J = 7$ Hz, OCH_2CH_3), 4.769 (d, 1H, CH), 4.165 (bs, 1H, NH), 6.609–7.29 (m, 10H, C_6H_5); ^{13}C NMR ($CDCl_3$, TMS): δ 16.24, 16.29, 16.43, 16.47, 54.82, 55.24, 56.03, 63.21, 63.25, 77.03, 113.91, 114.06, 118.36, 127.72, 128.98, 146.45, 159.34.

Diethyl(phenylamino)(2-chlorophenyl)methylphosphonate (C)

IR (KBr), 3236, 1235, 1016, 754 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 1.090 (t, 3H, $J = 7$ Hz, OCH_2CH_3), 1.362 (t, 3H, $J = 7$ Hz, OCH_2CH_3), 3.923 (q, 2H, $J = 7$ Hz, OCH_2CH_3), 4.230 (q, 2H, $J = 7$ Hz, OCH_2CH_3), 5.00 (bs, 1H, NH), 5.410 (d, 1H, CH), 6.605–7.603 (m, 10H, C_6H_5); ^{13}C NMR ($CDCl_3$, TMS): δ 16.32, 51.01, 52.23, 63.45, 77.02, 113.56, 118.54, 127.37, 129.09, 134.21, 145.80.

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